3D imaging of Sox2 enhancer clusters in embryonic stem cells.

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Public Summary:
Combinatorial cis-regulatory networks encoded in animal genomes represent the foundational gene expression mechanism for directing cell-fate commitment and maintenance of cell identity by transcription factors (TFs). However, the 3D spatial organization of cis-elements and how such sub-nuclear structures influence TF activity remain poorly understood. Here, we combine lattice light-sheet imaging, single-molecule tracking, numerical simulations, and ChIP-exo mapping to localize and functionally probe Sox2 enhancer-organization in living embryonic stem cells. Sox2 enhancers form 3D-clusters that are segregated from heterochromatin but overlap with a subset of Pol II enriched regions. Sox2 searches for specific binding targets via a 3D-diffusion dominant mode when shuttling long-distances between clusters while chromatin-bound states predominate within individual clusters. Thus, enhancer clustering may reduce global search efficiency but enables rapid local fine-tuning of TF search parameters. Our results suggest an integrated model linking cis-element 3D spatial distribution to local-versus-global target search modalities essential for regulating eukaryotic gene transcription.

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